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From: Robert Baan
Sent: Fri 11/20/2015 11:01:13 AM
Subject: Re: Documents on Mechanisms
2015 Krewski et al Mechanisms of Carcinogenesis November 18.pdf

Dear all,

I thank those of you who have submitted comments on the documents that we sent around previously.

Further to my message of November 9, I herewith send you the final document on 'Mechanisms of carcinogenesis', which I received from Dan Krewski yesterday.

This completes the set of three contributions on mechanisms from Dan's group.

On October 25 you received the two documents on concordance (Krewski *et al.*, Grosse *et al.*).

We hope to be able to soon organize a teleconference to discuss these contributions. Please send your comments to me, so that I can collate them in preparation of the telecon.

Best wishes to all,

Robert

From: Robert Baan

Sent: Monday, November 9, 2015 1:21 PM

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Subject: Documents on Mechanisms

Dear all,

I would like to thank several of you for sending their comments on the two documents on the concordance analyses (Grosse *et al.*, Krewski *et al.*) that we sent around two weeks ago (see message below). May I encourage others to also provide comments in writing so that we can prepare a final discussion during the teleconference.

With regards to the mechanistic data, I herewith attach two background documents for your perusal: 'Development of a database of toxicological endpoints and key characteristics of 86 agents known to cause cancer in humans' by Al-Zoughool *et al.*, and 'Overview of carcinogenic mechanisms for 109 agents known to cause cancer in humans' by Birkett *et al.*

The documents are in pdf-format, before editing.

A third document, 'Key characteristics of human cancer: an analysis of 86 agents known to cause cancer in humans' by Krewski *et al.* contains the results of the statistical analysis of the mechanistic data. We hope to send you that document soon.

With my best regards,

Robert

From: Robert Baan

Sent: Sunday, October 25, 2015 8:05 PM

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Subject: Results of Concordance Analysis

Dear colleagues,

First, I would like to thank the contributors of individual Chapters for their efforts to finalize and submit their documents for the Scientific Publication on 'Tumour Concordance and Mechanisms of Carcinogenesis'. Some 20 Chapters are safely in our files in final form. We count on the authors of the two missing Chapters to submit their contributions soon!

I am pleased to send you herewith attached two documents, including supplementary material, prepared by Dan Krewski and his team in close collaboration with the colleagues at the IARC, on the 'Concordance' part of the project.

The paper by Grosse *et al.* describes the development of a database of human and experimental animal tumours for the IARC Group-1 carcinogens, presented as an extensive Excel Table, initially compiled by Yann Grosse and Pascale Lajoie at the IARC, and refined and completed over the past months. The text of the paper describes the criteria for the comparison of human and animal tumour data, which require *sufficient evidence* of carcinogenicity, both in humans and in experimental animals. This means that Group-1 agents with *limited evidence* or *inadequate evidence* in humans, or with *limited evidence* or *inadequate evidence* in experimental animals are *a priori* not included in the comparison for tumour concordance. The analysis of tumour-site concordance requires assignment of a target site (organ or organ system) for tumour formation in humans and a target site in experimental animals. In this case, there is a set of Group-1 agents for which the animal evidence overall is *sufficient*, but no organ site could be identified, *e.g.*, because the evidence came from tumours in diverse organs. Also these agents were not included in the analysis. Since 'empty cells raise questions' in an Excel Table, an effort was made to precisely define - in the 'Comments' column of the Table - why a particular agent was excluded from analysis.

The paper by Krewski *et al.* gives an extensive description of the approach taken to analyze the

concordance data, the details on the exclusion of a number of agents, and the results of the bio-statistical analyses on the 'eligible' agents, with bar graphs and heat-maps. An important overall conclusion seems to be that all Group-1 agents with *sufficient evidence* of carcinogenicity in humans have also provided *sufficient* or *limited* evidence of carcinogenicity in one or more animal species.

We hope to send you the documents for the 'Mechanisms' part of the Vol100+-project soon.

We intend to organize a telephone conference with you all, to discuss the 'Concordance' and the 'Mechanisms' documents. On the basis of the outcome of these discussions we hope to be able to draft a 'consensus statement' on behalf of the Workshop participants. May I ask you to send us by email, before the teleconference, your comments, corrections, or suggestions for change on/in the attached 'Concordance' documents, and - in due course - on the 'Mechanisms' papers.

We hope to contact you soon again.

With my best regards,

Robert